

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number
WO 2004/096224 A3

(51) International Patent Classification⁷: **A61K 31/496**,
31/517, A61P 35/00, A61K 31/404

(21) International Application Number:
PCT/EP2004/004363

(22) International Filing Date: 24 April 2004 (24.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03009587.1 29 April 2003 (29.04.2003) EP
04000508.4 13 January 2004 (13.01.2004) EP
04001171.0 21 January 2004 (21.01.2004) EP

(71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only): **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(71) Applicant (for DE only): **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HILBERG, Frank** [DE/AT]; Pilgramgasse 18/22, A-1050 Wien (AT). **SOLCA, Flavio** [CH/AT]; Gesslgasse 10/6, A-1230 Wien (AT). **STEFANIC, Martin Friedrich** [DE/DE]; Am Weiher 25, 88447 Warthausen-Birkenhard (DE). **BAUM,**

Anke [DE/AT]; Groisbach 13, A-2534 Alland (AT). **MUNZERT, Gerd** [DE/DE]; Merianweg 64, 89075 Ulm (DE). **VAN MEEL, Jacobus, C.A.** [NL/AT]; Kärntnergasse 6, A-2340 Mödling (AT).

(74) Common Representative: **Boehringer Ingelheim International GMBH**; Binger Strasse 173, 55216 Ingelheim (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
16 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING CELL PROLIFERATION, MIGRATION OR APOPTOSIS OF MYELOMA CELLS, OR ANGIOGENESIS

(57) Abstract: The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amounts of specific active compounds and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compounds and/or radiotherapy for the manufacture of corresponding pharmaceutical combination preparations.



WO 2004/096224 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004363

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/496 A61K31/517 A61P35/00 A61K31/404

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/069299 A1 (WEYER-CZERNILOFSKY ULRIKE ET AL) 10 April 2003 (2003-04-10) page 1, left-hand column, lines 1-26	1-7
X	WO 03/011837 A (ARRINGTON KENNETH L ; HOFFMAN WILLIAM F (US); FRALEY MARK E (US); MERC) 13 February 2003 (2003-02-13) page 74, lines 13-20; claims	1-9, 13-15, 19, 21-23, 26, 27, 30
X	WO 03/022815 A (LIANG CONGXIN ; TANG PENG CHO (US); BLAKE ROBERT A (US); GUAN HUIPING) 20 March 2003 (2003-03-20) page 3, lines 15-31 page 19, line 26 - page 20, line 4 page 27, line 27 - page 30, line 3 ----- -/--	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

29 October 2004

Date of mailing of the international search report

05/11/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Venturini, F

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP2004/004363

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/070008 A (IMCLONE SYSTEMS INC ; ROCKWELL PATRICIA (US); GOLDSTEIN NEIL I (US)) 12 September 2002 (2002-09-12) cited in the application the whole document	1-9, 13-15, 19, 21-23, 26,27,30
P,X	DE 102 33 500 A (BOEHRINGER INGELHEIM PHARMA) 19 February 2004 (2004-02-19) the whole document	1-15
X	WO 01/32651 A (HENNEQUIN LAURENT FRANCOIS AND ; THOMAS ANDREW PETER (GB); ASTRAZENECA) 10 May 2001 (2001-05-10) page 26, line 22 - page 28, line 4 claims	1-10, 13-15
X	US 6 306 874 B1 (ARRINGTON KENNETH L ET AL) 23 October 2001 (2001-10-23) column 27, line 10 - column 29, line 40; claims	1-9, 13-15, 19, 21-23, 26,27,30
P,A	WO 03/065995 A (LYONS JOHN ; SUPERGEN INC (US); RUBINFELD JOSEPH (US)) 14 August 2003 (2003-08-14) the whole document	1-30
A	WO 98/54156 A (MYERS MICHAEL ; PERSONS PAUL E (US); SPADA ALFRED P (US); MAGUIRE MART) 3 December 1998 (1998-12-03) the whole document	1-30
A	DE 199 24 401 A (BOEHRINGER INGELHEIM PHARMA) 30 November 2000 (2000-11-30) the whole document	1-30
A	DE 100 42 696 A (BOEHRINGER INGELHEIM PHARMA) 14 March 2002 (2002-03-14) the whole document	1-30
A	WO 97/41844 A (ALCON LAB INC ; CLARK ABBOT F (US); DOSHI RUPA (US)) 13 November 1997 (1997-11-13) the whole document	1-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP/EP2004/004363

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2003069299	A1	10-04-2003	DE 10054019 A1	23-05-2002
			US 2004044222 A1	04-03-2004
			US 2004044053 A1	04-03-2004
			AU 1598002 A	15-05-2002
			WO 0236564 A1	10-05-2002
			EP 1341760 A1	10-09-2003
			JP 2004513113 T	30-04-2004
WO 03011837	A	13-02-2003	WO 03011837 A1	13-02-2003
WO 03022815	A	20-03-2003	BR 0212435 A	17-08-2004
			CA 2459879 A1	20-03-2003
			EP 1436259 A1	14-07-2004
			WO 03022815 A1	20-03-2003
			US 2003119819 A1	26-06-2003
WO 02070008	A	12-09-2002	US 2003103973 A1	05-06-2003
			BG 108214 A	30-09-2004
			CA 2439933 A1	12-09-2002
			CZ 20032586 A3	18-08-2004
			EE 200300428 A	15-10-2004
			EP 1379276 A1	14-01-2004
			HU 0303378 A2	29-12-2003
			NO 20033856 A	03-11-2003
			WO 02070008 A1	12-09-2002
			US 2003108545 A1	12-06-2003
DE 10233500	A	19-02-2004	DE 10233500 A1	19-02-2004
			WO 2004013099 A1	12-02-2004
			US 2004176392 A1	09-09-2004
WO 0132651	A	10-05-2001	AU 769222 B2	22-01-2004
			AU 1288601 A	14-05-2001
			BG 106659 A	31-03-2003
			BR 0015203 A	16-07-2002
			CA 2389767 A1	10-05-2001
			CN 1387527 T	25-12-2002
			CZ 20021526 A3	17-07-2002
			EE 200200237 A	16-06-2003
			EP 1244647 A1	02-10-2002
			WO 0132651 A1	10-05-2001
			HU 0203453 A2	28-05-2003
			JP 3522727 B2	26-04-2004
			JP 2003513089 T	08-04-2003
			NO 20022139 A	03-05-2002
			NZ 518028 A	26-03-2004
			PL 355942 A1	31-05-2004
			SK 6122002 A3	09-01-2003
			ZA 200202775 A	03-12-2003
US 6306874	B1	23-10-2001	AU 1571001 A	30-04-2001
			BG 106710 A	31-03-2003
			BR 0014843 A	11-06-2002
			CA 2387351 A1	26-04-2001
			CN 1409708 T	09-04-2003
			CZ 20021390 A3	11-09-2002
			EE 200200201 A	16-06-2003
			EP 1226136 A2	31-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP/EP2004/004363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6306874	B1	HR 20020349 A2	29-02-2004
		HU 0203323 A2	28-02-2003
		JP 2003512369 T	02-04-2003
		NO 20021820 A	23-05-2002
		NZ 518001 A	28-05-2004
		PL 354292 A1	29-12-2003
		SK 6912002 A3	05-08-2003
		TR 200201051 T2	23-09-2002
		WO 0129025 A2	26-04-2001
		US 6794393 B1	21-09-2004
		ZA 200202985 A	16-04-2003
WO 03065995	A 14-08-2003	US 2003147813 A1	07-08-2003
		US 2004127453 A1	01-07-2004
		CA 2474174 A1	14-08-2003
		WO 03065995 A2	14-08-2003
WO 9854156	A 03-12-1998	AU 747026 B2	09-05-2002
		AU 7706298 A	30-12-1998
		AU 751188 B2	08-08-2002
		AU 7707998 A	30-12-1998
		AU 742739 B2	10-01-2002
		AU 7803798 A	30-12-1998
		BG 103963 A	31-07-2000
		BG 103965 A	31-07-2000
		BG 104006 A	31-07-2000
		BR 9809172 A	01-08-2000
		BR 9809501 A	20-06-2000
		BR 9809515 A	20-06-2000
		CA 2291728 A1	03-12-1998
		CA 2291750 A1	03-12-1998
		CA 2291774 A1	03-12-1998
		CN 1261353 T	26-07-2000
		CN 1280572 T	17-01-2001
		CN 1140516 C	03-03-2004
		EA 2600 B1	27-06-2002
		EA 4103 B1	25-12-2003
		EP 0991628 A1	12-04-2000
		EP 1001945 A1	24-05-2000
		EP 1001946 A1	24-05-2000
		HU 0002084 A2	28-10-2000
		HU 0002219 A2	28-12-2000
		HU 0004807 A2	28-11-2001
		JP 2002513417 T	08-05-2002
		JP 2002500675 T	08-01-2002
		JP 2002500676 T	08-01-2002
		NO 995817 A	26-11-1999
		NO 995818 A	26-11-1999
		NO 995819 A	26-11-1999
		OA 11264 A	19-11-2002
		OA 11221 A	16-07-2003
		OA 11222 A	16-07-2003
		PL 337084 A1	31-07-2000
		PL 337086 A1	31-07-2000
		PL 337087 A1	31-07-2000
		SK 157999 A3	12-06-2000
		SK 158099 A3	12-06-2000
		SK 158199 A3	12-06-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/004363

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9854156	A		WO 9854156 A1	03-12-1998
			WO 9854157 A1	03-12-1998
			WO 9854158 A1	03-12-1998
DE 19924401	A	30-11-2000	DE 19924401 A1	30-11-2000
			AU 5215700 A	18-12-2000
			WO 0073297 A1	07-12-2000
DE 10042696	A	14-03-2002	DE 10042696 A1	14-03-2002
			AU 1023301 A	23-04-2001
			BG 106587 A	31-01-2003
			BR 0014735 A	16-07-2002
			CA 2387013 A1	19-04-2001
			CN 1391557 T	15-01-2003
			CZ 20021410 A3	17-07-2002
			EE 200200197 A	16-06-2003
			WO 0127081 A1	19-04-2001
			EP 1224170 A1	24-07-2002
			HR 20020306 A2	31-10-2003
			HU 0204587 A2	28-05-2003
			JP 2003511441 T	25-03-2003
			MX PA02002799 A	27-02-2003
			NO 20021719 A	11-04-2002
			PL 355433 A1	19-04-2004
			SK 6462002 A3	06-08-2002
			US 6762180 B1	13-07-2004
WO 9741844	A	13-11-1997	AU 2438297 A	26-11-1997
			WO 9741844 A1	13-11-1997